Nos. 14-1361, -1366
UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

IN RE BRCA1- AND BRCA2- BASED HEREDITARY CANCER TEST PATENT LITIGATION
UNIVERSITY OF UTAH RESEARCH FOUNDATION, THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA, HSC RESEARCH AND DEVELOPMENT LIMITED PARTNERSHIP, ENDORECHERCHE, INC., AND MYRIAD GENETICS, INC.

Plaintiffs-Appellants,

v.

AMBRY GENETICS CORPORATION,

Defendant-Appellee.

Appeal from the United States District Court for the Central District of Utah in consolidated case no. 2:13-cv-00640, Judge Robert J. Shelby.

DEFENDANT-APPELLEE'S CORRECTED BRIEF

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UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

University of Utah v. Ambry Genetics Corporation

No. 14-1361; -1366

CERTIFICATE OF INTEREST

Counsel for the appellee, Ambry Genetics Corporation, certifies the following (use "None" if applicable; use extra sheets if necessary):

1. The full name of every party or amicus represented by me is:

Ambry Genetics Corporation

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

Named Party, Ambry Genetics Corporation, is the real party in interest

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

None

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

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June 2, 2014
Date

/s/ M. Miller Baker
Signature of counsel
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STATEMENT OF RELATED CASES

The MDL proceeding from which these interlocutory appeals have been taken includes patent infringement suits by Plaintiffs-Appellants against other defendants involving the same patents at issue here. The decision in these appeals is likely to affect those other suits.

This Court's decision in the pending appeals in *Ariosa Diagnostics, Inc., et al. v. Sequenom, Inc., et al.*, Nos. 14-1139, 14-1142, and 14-1144 may affect this Court's decision in this matter, and vice-versa.

STATEMENT OF ISSUES

1. Whether the district court abused its discretion in finding Myriad would suffer irreparable harm absent a preliminary injunction when the district court relied on Myriad's misrepresentation concerning the expiration date of its patents and when subsequent events have disproved Myriad's predictions of price erosion and lost market share.

2. Whether the district court abused its discretion in finding that Ambry raised a substantial question that composition claims 16 and 17 of the '282 patent and claims 29 and 30 of the '492 patent are directed to patent-ineligible subject matter where the claims read on segments of man-made DNA that have the same composition and sequence of nucleic acid chains found in naturally occurring, patent-ineligible DNA.

3. Whether—if such claims are not yet moot due to either the expiration of the patent on August 12, 2014 as represented by Myriad or the actual expiration of the patent on January 20, 2015—the district court abused its discretion in finding that Ambry raised a substantial question that method claims 7 and 8 of the ’441 patent are directed to patent-ineligible subject matter where the dependent claims (a) merely append to the previously invalidated, patent-ineligible parent claim well-understood, routine, conventional activity previously engaged in by those in the field, and (b) tie using unpatentable subject matter to well-understood, routine, conventional activity, previously engaged in by those in the field to preempt all practical access to patent-ineligible abstract mental processes, human genes, and the information they encode.

4. Whether, by not briefing the issue, Myriad waived its right to appeal the district court’s finding that Ambry raised a substantial question that method claims 2 and 4 of the ’155 patent are directed to patent-ineligible subject matter, and if not so waived, whether the district court abused its discretion in finding that Ambry had raised a substantial question that the claims are directed to patent-ineligible subject matter.

5. Whether the district court abused its discretion in finding that the balance of the hardships favored Ambry because a preliminary injunction would cause destruction of its business.

6. Whether the district court abused its discretion in finding that the public interest did not weigh in favor of either party.

INTRODUCTION

The district court denied Plaintiffs-Appellants' (collectively "Myriad") application for a preliminary injunction, finding in favor of the Defendant-Appellee ("Ambry") on two of the four requirements for preliminary injunctive relief—likelihood of success on the merits and balancing of the harms—and finding in favor of neither party as to a third requirement, the public interest. Only as to one requirement—irreparable harm—did the district court find in favor of Myriad. But on that issue, the district court's finding was tainted by reliance on Myriad's material misrepresentation regarding the expiration date of its patents.

The district court did not abuse its discretion in determining that Myriad had not established any of the three remaining requirements. Moreover, the district court's determination that Myriad would suffer irreparable harm was an abuse of discretion in light of Myriad's misrepresentation to the district court and subsequent admissions by Myriad. For the reasons provided below, this Court should affirm the district court's denial of the preliminary injunction.

STATEMENT OF THE CASE

A. Technological Background

1. Genes and DNA

The informational content of DNA is preserved and passed on through complementary Watson-Crick base pairing. (A6306-09 ¶¶ 28-35.) Natural DNA replication relies on Watson-Crick base pairing to replicate copies of single-stranded DNA. (A6309-11 ¶¶ 36-38; A2788-89 ¶ 32.) The cell utilizes single-stranded copies of DNA during transcription as a template for mRNA, the synthesis of which also requires Watson-Crick base pairing. (A6313-14 ¶¶ 43-46; A2789 ¶¶ 33, 34.)

The functional properties of DNA are the same no matter how DNA is isolated. (A6303-04 ¶¶ 16-17, 19; A6316-17 ¶¶ 52-54.) The informational content of "isolated DNA," including synthesized DNA, is the same as naturally occurring DNA. (A6323-24 ¶ 63.) DNA chemically synthesized in the laboratory is treated the same as "native DNA" by cells. (A6303-04 ¶¶19-21; A6306 ¶ 27; A8897 at 115:8-24.)

2. Standard Laboratory Techniques to Study Genes as of the Patents' Priority Date

Myriad's method claims are directed to comparing the sequence of the native DNA obtained from a patient sample to a reference DNA sequence that is either a wild-type or altered version of a predetermined *BRCA1* or *BRCA2*

sequence. (A2783 ¶ 19.) Each of the claims generally recites steps or limitations related to preparing and observing the patient sample in determining the sequence of the DNA obtained from a patient sample. These related steps include "hybridization," "amplification," and/or "sequencing" of the patient sample and were well known in the art. (A2784 ¶ 21; A7526-27 ¶ 5.)

Nucleic acid hybridization is the noncovalent association of two complementary strands of nucleic acid that occurs via the inherent chemical properties of the nucleic acid strands, specifically, the sequence of nucleotide subunits. (A2784-85 ¶¶ 22-23.) In nature, hybridization causes double-stranded DNA to have its characteristic double-helical structure. (A2784 ¶ 22.)

Probes. In the lab, researchers incubate single-stranded segments of DNA called "probes" with their targets to determine the presence (if the probes hybridize) or absence (if they do not) of specific DNA sequences in a sample. (A2784-85 ¶ 23.)

Primers. Scientists also routinely use single-stranded segments of DNA as primers for "amplification" (copying) of a DNA segment and in nucleic acid sequencing (both discussed below). Primers comprise chemically synthesized isolated DNA with sequences indistinguishable from the native DNA sequences and are used for amplification. (A6324-25 ¶¶ 66-68.) DNA primers associate with target DNA through Watson-Crick base pairing and become integrated into an

identical copy of the DNA segment targeted. (A6324-25 ¶¶ 67-68; A7616-17 ¶¶ 13-17.) The resulting amplicon(s) comprise DNA molecules that are exact copies of the natural DNA template harvested from a cell. (A6338-39 ¶¶ 105-107; A7623-24 ¶¶ 34-35.)

Scientists design primers and probes to be exactly complementary to a template strand because successful amplification or probe hybridizations requires exact complementarity in order for the primers and probes to Watson-Crick base pair with their targets. (A6341 ¶ 113; A7613-15 ¶¶ 6-11; A2785-86 ¶¶ 24-25; A8887-90 at 105:18-108:3; A8898 at 116:21-24; A8899 at 117:8-16.) Scientists were routinely creating and using DNA probes and primers by the earliest filing date of the patents at issue. (A2786 ¶ 26.)

Amplification allows a scientist to copy relevant segments of DNA required to use contemporary DNA detection protocols or DNA sequence-reading instrumentation. (A6324 ¶¶ 64-65.) Amplification of the gene segment is required because a "magic microscope" to observe a DNA sequence directly does not exist. (A6325-26 ¶¶ 69-70.) The polymerase chain reaction (PCR) is used to "isolate" DNA by making identical copies of the target sequence. (A6303 ¶ 16.) PCR relies on Watson-Crick base pairing, and scientists use standard biochemical techniques to detect specific sequences within the PCR product. (A6303 ¶ 18.) DNA isolated by PCR must maintain its fidelity for testing and subsequent

manipulation or investigation in a lab. (A6317-22 ¶¶ 55-58; A8893-94 at 111:20-112:17.)

Sequencing refers to determining the exact nucleotide sequence of one or more segments of DNA using one of a variety of laboratory techniques. A technique called "Sanger Sequencing" (also referred to as "dideoxy sequencing") was the most prevalent sequencing technique in modern labs by the time Myriad had applied for the first of the patents asserted in its Motion for Preliminary Injunction. (A2790 ¶ 35.) Like PCR, Sanger Sequencing utilizes primers (and other reagents) and depends on Watson-Crick base pairing. (A2790 ¶ 35.) Next Generation sequencing is a new technique for sequencing DNA developed after the asserted patents were filed. (A8898 at 116:4-12.)

The laboratory techniques used to perform the complementary tasks of hybridization, amplification, and sequencing to observe a native gene sequence in a patient sample were well understood, widely used, and fairly uniform where any scientist engaged in obtaining the sequence of a gene in a patient sample would have relied (and would have had to rely) on the same techniques and general approach as of the date the patents were filed. (A2791 ¶ 37; A7527-29 ¶¶ 6-12; A8900 at 118:10-24; A9024-25 at 242:25-243:22.)

B. The *AMP* Litigation Involving the Patents on Appeal

1. Judge Sweet Rejects Myriad's Position that DNA Primers Constitute Patentable Subject Matter

The '282, '441 and '492 patents at issue here were also at issue in the litigation that culminated in *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013) ("*AMP III*"). The plaintiffs in the *AMP* litigation challenged the patent eligibility of *BRCA* "isolated DNA" composition claims and method claims for comparing *BRCA* sequences.

During claim construction, Judge Sweet adopted the patents'—and Myriad's—definition of "isolated DNA," construing "isolated DNA" to "*include both DNA originating from the cell as well as DNA synthesized through chemical or heterologous biological means*." *Ass'n for Molecular Pathology v. USPTO*, 702 F. Supp. 2d 181, 217 (S.D.N.Y. 2010) ("*AMP I*") (emphasis added); *see also* A174 at 19:8-18, A370 at 17:62-18:5. Myriad never disputed its own patents' definition that isolated DNA could be DNA synthesized in a laboratory. *AMP I*, 702 F. Supp. 2d at 216-17.

Judge Sweet rejected Myriad's attempts to distinguish "isolated DNA" of its composition claims from natural DNA. Myriad contended that isolated DNA constituted a non-natural molecule with new utilities. Judge Sweet held that isolated DNA's use as primers and probes did not preserve the patent-eligibility of isolated DNA because isolated DNA comprised natural DNA sequence. He

recognized that "the basis for [a probe or primer's] utility is the fact that the isolated DNA possesses the *identical nucleotide sequence* as the target [genomic] DNA sequence, thus allowing target specific hybridization between the DNA primer and the portion of the target DNA molecule possessing the corresponding sequence." *AMP I*, 702 F. Supp. 2d at 231 (emphasis added). He found method claim 1 of the '441 patent invalid because it was a patent-ineligible abstract mental comparison of two DNA sequences and even if the claims included "transformations" of isolating and sequencing DNA, these purported transformations were only data gathering steps." *Id.* at 236.

2. The Federal Circuit's *AMP II* Decision

The Federal Circuit affirmed-in-part and reversed-in-part. *Ass'n for Molecular Pathology v. USPTO*, 689 F.3d 1303, 1328 (Fed. Cir. 2012) ("*AMP II*"). This Court upheld Judge Sweet's ruling on the '441 patent method claim 1, but reversed his ruling that the "isolated" DNA compositions of the '282 and '492 patents were patent ineligible. *Id*.

3. The Supreme Court's *AMP III* Decision Holds that Isolated DNA Segments that Include Primers and Probes Are Unpatentable Products of Nature

In the Supreme Court, the *AMP* plaintiffs challenged only *AMP II's* ruling on the isolated DNA composition claims. In defense of that ruling, Myriad argued that a DNA "primer" and a "probe" were "isolated DNA molecule[s]" with

different characteristics reflecting human ingenuity and thus was not a product of nature:

- "Two critical uses of the claimed molecules [isolated DNA] are to 'probe' for target DNA in a patient sample or to 'prime' the production of copies of the target DNA in the laboratory." (A6222.)
- "[A]n isolated DNA molecule can be used as a cancer-mutation-detecting probe or primer because of natural qualities (their ordering of nucleotides, which in some cases other than cDNA molecules follows the ordering of native nucleotides) in combination with the inventors' scientific work and ingenuity in characterizing and defining the molecule's starting and end points. . . ." (A6256.)
- "As a 'primer,' the isolated DNA molecule is used in a reiterative process called a polymerase chain reaction ('PCR')." (A6223 n.3.)
- "Long strands of isolated DNA molecules are useful as probes and PCR templates." (A6257 n.11.)

A unanimous Supreme Court rejected Myriad's arguments and held that the isolated DNA claims (*e.g.*, primers and probes) were not patent eligible.[1] *AMP III*, 133 S. Ct. at 2111. The Supreme Court held that a "segment" of DNA that corresponds to the naturally occurring sequence is not patent eligible by its "isolation" from the genomic DNA. *Id*. The Court understood that isolated DNA (including primers and probes) could be chemically synthesized and was "technically" a new molecule, quoting Judge Lourie. *Id*. at 2115 ("Isolated DNA . . . is *synthesized* to consist of just a fraction of a naturally occurring DNA molecule."). But such synthesized DNA molecules at issue in *AMP III* were not

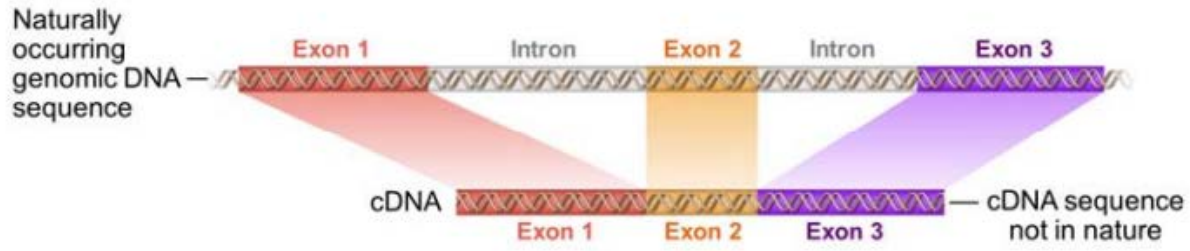
[1] This unanimous holding was consistent with the position advocated by the United States. (A5919.)

"markedly different" from the natural DNA under the Supreme Court's prior decision in *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), which Myriad "recognize[d]" was "central to this inquiry." *AMP III*, 133 S. Ct. at 2116-17. Nor did Myriad's isolated DNA claims rely "in any way on the chemical changes that result from the isolation of a particular section of DNA." *Id.* at 2118.

Instead, the isolated DNA claims were "*primarily concerned with the information contained in the genetic sequence*, not with the specific chemical composition of a particular molecule." *Id*. (emphasis added). The Supreme Court concluded: "We merely hold that genes *and the information they encode* are not patent eligible under § 101 simply because they have been isolated from the surrounding genetic material." *Id*. at 2120 (emphasis added).

As to the cDNA claims, Myriad argued they were patent eligible because a cDNA molecule is a DNA molecule "with a sequence nowhere found in native DNA." (*E.g.*, A6251.) The Court agreed, in part, initially stating cDNA did not pose the same obstacles to patentability "as naturally occurring, isolated DNA segments." *AMP III*, 133 S. Ct. at 2119. The Court found that the lab technician who makes a cDNA might make a new, patent-eligible DNA composition. *Id*. cDNA is patent eligible, for example, when the lab technician creates a synthetic molecule juxtaposing two exonic sequences that are separated in nature by intervening intronic sequence. *Id.* Such a molecule is not a product of nature

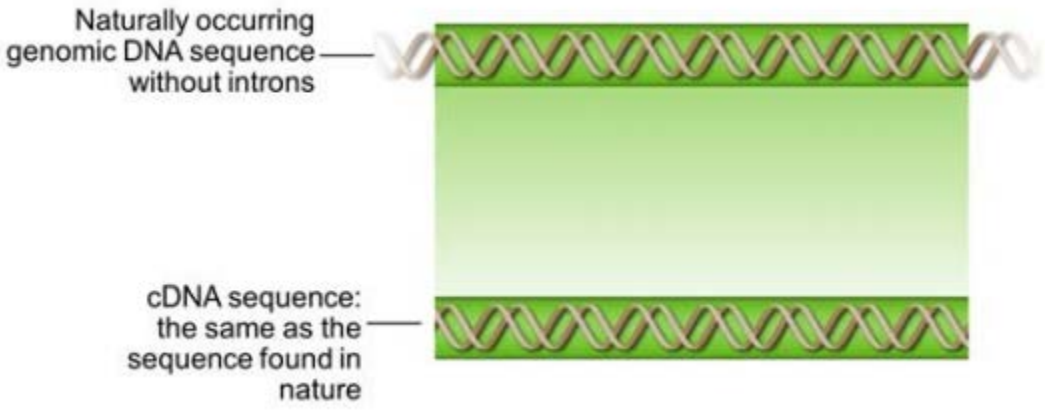
because the sequence in the synthesized molecule differs from what is found in nature. An example of this cDNA construct is depicted below:



If the lab technician makes a cDNA molecule that spans only a single exon or portion thereof, then that cDNA is not patent eligible because it is "indistinguishable" from natural DNA, *viz.*:

> As a result, cDNA is not a "product of nature" and is patent eligible under §101, *except insofar as very short series of DNA may have no intervening introns to remove when creating cDNA. In that situation, a short strand of cDNA may be indistinguishable from natural DNA.*

Id. (emphasis added). An example of this type of cDNA construct is depicted below:



C. The District Court Proceedings Below

One month after the *AMP III* opinion issued, and despite having argued and unanimously lost on the issue that primer and probe "isolated DNA" was patent-eligible subject matter whether chemically synthesized or not, Myriad sued Ambry and sought a preliminary injunction on claims containing the identical subject matter, namely claims 29 and 30 of the '492 patent related to the *BRCA2* genes and claims 16 and 17 of the '282 patent related to the *BRCA1* genes. Myriad further asserted six claims from four method patents related to the comparison of *BRCA1* and *BRCA2* gene sequences, including claims from the '441 and '857 patents that depend from claims this Court in *AMP II* found to be patent ineligible.

As part of its analysis on both the patent eligibility of the asserted claims and irreparable harm, the district court considered declarations and live testimony from numerous fact and expert witnesses. As to the primer claims, the district court looked to Supreme Court precedent and concluded that the claimed primers were not patent eligible. Despite Myriad's suggestion, the district court did not extend the Supreme Court's holding in *AMP III*. Instead, the court thoroughly reviewed the prior litigation involving the patents at issue in both this appeal and the *AMP* litigation, as well as other admittedly relevant Supreme Court authority. (A76-87.) The district court concluded that Ambry raised substantial questions on the DNA primer sequence claims based on both *AMP III* alone, in addition to the Supreme

Court's decisions in *Chakrabarty* and *Funk Brothers Seed Co. v. Kalo Innoculant Co.*, 333 U.S. 127 (1948).

Like invalidated independent claim 1 of the '441 patent, its dependent claims 7 and 8 are directed to "[a] method for screening germline of a human subject for an alteration of a *BRCA1* gene *which comprises comparing* germline sequence of a *BRCA1* gene … with germline sequences of wild-type *BRCA1* gene..." (A348.) That is, each of the claims is to a comparison, an abstract mental process. Claims 7 and 8 do not recite "a new method of processing a patient sample to diagnose cancer risk," as Myriad contends. (Myriad Br. at 35.) The claims also recite laws of nature in that they refer to the patent-ineligible *BRCA* genes and the information they encode.

The district court performed a thorough analysis of the method claims' patent eligibility based on the largely undisputed and case-specific facts before it. "Despite the striking initial similarities to the five patent ineligible method claims" in Myriad's previous litigation, the district court followed the controlling law and "viewed [each claim] as a whole." (A92, A97-98.) The court followed the guidance provided in relevant precedents, including *AMP II* and the following Supreme Court decisions: *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012); *Diamond v. Diehr*, 450 U.S. 175 (1981); and *Parker v. Flook*, 437 U.S. 584 (1978). The district court addressed and

rejected Myriad's arguments that method claims applying well-known and routine steps to newly discovered *BRCA* sequences rendered those claims patent eligible. (A93-100.) The court concluded that Myriad's asserted method claims were patent ineligible because (i) they did not set forth an "inventive step," other than the ineligible portions of the claim, that was beyond well-understood, routine, conventional activity previously engaged in by those in the field, and (ii) the claims risked preemption of the patent-ineligible subject matter itself. (A88-100.)

SUMMARY OF THE ARGUMENT

The district court determined that Myriad did not establish three of the four requirements for preliminary injunctive relief: likelihood of success on the merits on patent eligibility[2]; that the balance of the hardships favored Myriad; and that injunctive relief serves the public interest. If this Court affirms the district court regarding any of these three requirements, it must affirm the denial of preliminary injunctive relief. And if this Court concludes that the district court abused its discretion in finding that Myriad had established the fourth requirement for preliminary injunctive relief, irreparable harm, then this Court must affirm the district court's denial of such relief—regardless of its conclusions as to the three other requirements.

[2] The district court did not reach the questions of patentability under Sections 102 and 103 and infringement. (A69-70.)

1. Irreparable Harm. In finding irreparable harm, the district court relied on Myriad's misrepresentation that its patents "begin to expire" in August 2014, when the earliest such expiration is actually January 20, 2015. Standing alone, this renders the district court's determination of irreparable harm an abuse of discretion, because it taints the entire finding. Subsequent developments of which this Court can take judicial notice disprove the district court's findings that price erosion and lost market share also contribute to irreparable harm.

2. Likelihood of Success on the Merits on Patent Eligibility.

a. '282/'492 Patent Composition Claims. The district court correctly found that Myriad has "reversed course" from its previous judicial representations that the term "isolated DNA" as used in Myriad's '282 patent includes synthetic DNA, like primers and probes. The district court made factual findings — which Myriad does not contest — that there are insubstantial structural and functional differences between the claimed primers and the patent-ineligible, naturally occurring DNA segments from which the claimed primers and probes are "derived from" or "isolated from." The function of the DNA primers as described in Myriad's patent claims does not differ from that of naturally occurring DNA. Primers merely bind to a complementary strand of DNA and "perform in their natural way" serving the "ends nature originally provided."

b. ’441 Patent Method Claims. Myriad is judicially estopped from disputing that the ’441 patent expires on August 12, 2014, because Myriad has repeatedly represented that date as the applicable expiration date. Myriad’s motion for a preliminary injunction as to the ’441 patent’s two method claims therefore becomes moot on that date, or at the very latest, on January 20, 2015, when the ’441 patent actually expires.

If this Court otherwise reaches the merits of the ’441 patent’s method claims, it should hold that the district court did not abuse its discretion in finding that a substantial question exists as to their Section 101 eligibility. Based on its undisputed factual findings, the district court correctly concluded that these claims add nothing to the patent-ineligible subject matter other than well-understood, routine, and conventional activity previously engaged in by those in the field. The district court also correctly found that Myriad’s claims effectively build a wall around both the *BRCA1* and *BRCA2* genes themselves and the claimed mental processes. Myriad’s ’441 patent method claims are nothing more than a drafting effort designed to monopolize the law of nature itself.

c. ’155 Patent Method Claims. By not briefing these claims, Myriad waived its appeal with respect them. Instead of meeting its burden, Myriad asserted that the ’155 patent’s two method claims are “similar” to the ’441 patent’s

two method claims, even though the ’441 patent claims materially differ from the ’155 patent claims.

3. Balance of the Harms. Myriad does not dispute a key factual finding by the district court supporting its conclusion that the balance of the harms tips slightly in favor of Ambry: that Ambry exercised caution and only entered the market after the Supreme Court’s *AMP III* decision placed Myriad’s patents in substantial doubt. The district court’s tainted finding of irreparable harm further supports the district court’s conclusion that the balance of the hardships tilted in Ambry’s direction, as the tilt could only have been *more* pronounced had the district court known—contrary to Myriad’s representations—that Myriad’s patents begin to expire, at the earliest, in 2015.

4. The Public Interest. Myriad does not challenge the district court’s determinations that Myriad’s lifesaving tests are more expensive and generally less available than Ambry’s comparable lifesaving tests, and that Myriad has abused the patent system by refusing to disclose critical information relevant to further technological innovation. By contrast, to challenge the district court’s determination that the public interest supported neither side, Myriad merely argues that the public interest generally favors enforcing patents to encourage innovation.

STANDARD OF REVIEW

A district court abuses its discretion in denying a preliminary injunction only if the plaintiff, "in addition to showing the likelihood of success on the merits," has also shown that "it likely will suffer irreparable harm, that the balance of equities tips in its favor, and that an injunction is in the public interest." *Aria Diagnostics, Inc. v. Sequenom, Inc.*, 726 F.3d 1296, 1304 (Fed. Cir. 2013) (citing *Winter v. Natural Res. Def. Council, Inc.*, 555 U.S. 7, 20 (2008).

"[T]he analysis under § 101, while ultimately a legal determination, is rife with factual issues." *Ultramercial, Inc. v. Hulu, LLC*, 722 F.3d 1335, 1339 (Fed. Cir. 2013). The Court gives no deference to the district court's ultimate legal determination of patent ineligibility, but the Court may not disturb the district court's findings of fact that bear on that issue unless those findings are clearly erroneous. *See, e.g., Raytheon Co. v. United States*, 747 F.3d 1341, 1348 (Fed. Cir. 2014); Fed. R. Civ. P. 52(a)(6) (providing that reviewing court may not set aside findings of fact unless clearly erroneous). A finding of fact is clearly erroneous only "when on the entire record, the appellate court is left with a definite and firm conviction that a mistake has been committed." *In re Mark Indus.*, 751 F.2d 1219, 1222 (Fed. Cir. 1984) (internal quotations and citations omitted).

ARGUMENT

I. THE DISTRICT COURT'S FINDING OF IRREPARABLE HARM IS TAINTED BY MYRIAD'S MISREPRESENTATIONS AND HAS BEEN DISPROVEN BY SUBSEQUENT EVENTS

Myriad's misrepresentations concerning the expiration of its patents and subsequent developments have fatally undermined the district court's finding of irreparable harm. Accordingly, this Court may affirm the district court's denial of a preliminary injunction on the sole ground that Myriad will not be irreparably harmed, without the necessity of reaching the question of Myriad's likelihood of success on the merits. *Sequenom,* 726 F.3d at 1304 (preliminary injunction applicant must prevail on all four factors).

A. The District Court, Relying on Myriad's Representations, Found that the '441 and '282 Patents Expire in August 2014

The district court relied on Myriad's representations that the '441 patent and other patents began to expire in August 2014 as a ground for irreparable harm.[3] Myriad's preliminary injunction motion asserted that "[t]he patents-in-suit begin to expire in August 2014," arguing that "[t]his, in itself, provides ample basis for a finding of irreparable harm." (A1926.) The district court agreed that the patents will begin to expire in August 2014, and found that the '441 and '282 patents "have the priority date of August 12, 1994, and begin to expire in August 2014."

[3] Even if this finding of irreparable harm did not rest on a factual error, it was wrong as a matter of law because loss of exclusivity is not irreparable harm. *See Robert Bosch LLC v. Pylon Mfg. Corp.*, 659 F.3d 1142, 1149 (Fed. Cir. 2011).

(A27 n.10.)[4] Agreeing with Myriad, the district court concluded that this contributed to irreparable harm. (A61, A65-66.)

More recently, Myriad argued to *this* Court—without correcting the district court's determination that the patents expiring in August 2014 are the '441 and '282 patents—that the "patents-in-suit begin to expire in August 2014" which supported its motion to expedite this appeal. (ECF No. 19-1 at 5 (March 24, 2014).) In response, Ambry listed the expiration dates for all six of the patents-in-suit and noted that only one of them—the '441 patent—appeared to expire in August 2014.[5] (ECF No. 26 at 13 (Apr. 7, 2014).) In its reply, Myriad conceded that only "[o]ne patent expires in 2014" and did not dispute it is the '441 patent. (ECF No. 29 at 4 (Apr. 8, 2014).)

B. The '441 and '282 Patents Actually Expire in 2015

Myriad's representations regarding the expiration of its patents, and the district court's reliance on those representations, were erroneous. The '441 patent is due to expire on January 20, 2015. The '441 patent, which issued from application Ser. No. 08/488,011, lists January 5, 1996 as the filing date. (A250.) However, a certificate of correction reflects the application was filed on June 7,

[4] Myriad has never expressly identified *which* patent(s) begin to expire in 2014. Nevertheless, Myriad never corrected the district court's finding that the '441 and '282 patents expire in August 2014.

[5] As demonstrated below, Ambry was in error as to the '441 Patent, which expires in 2015.

1995. (A350.) As a pre-GATT filing, the patentee was afforded the longer of the 17 years from the issue date or 20 years from the earliest filed priority application. The ’441 patent issued on May 19, 1998, but was also subject to a terminal disclaimer to U.S. Patent App. Ser. No. 08/487,002, filed on June 7, 1995, which issued as U.S. Patent No. 5,710,001 on January 20, 1998. Because the latest expiration date for the ’001 patent is *January 20, 2015*, the ’441 patent also expires on that day.

The ’282 patent, which issued from application Ser. No. 08/483,554 filed on June 7, 1995, issued on May 5, 1998. The later of the two expiration dates for the ’282 patent is May 5, 2015.

As the ’441 and ’282 patents actually expire in 2015, the district court’s factual finding of earlier expiration dates is clearly erroneous, which in turn fatally infects the district court’s determination of irreparable harm based on that finding.

C. Subsequent Events Have Disproven the District Court’s Prediction of Irreparable Harm in the Form of Price Erosion and Lost Market Share

The district court based its finding of irreparable harm in part on its determination that competition would cause Myriad to suffer prior erosion and lost market share. (A62.) These predictions—based on evidence received in September and October 2013—have not come to pass in the ensuing seven months. Myriad’s subsequent statements to its investors establish that Myriad is enjoying

record revenues, notwithstanding competition by Ambry and others, and has downplayed to the investing public any harm from the ongoing competition.

On May 6, 2014, Myriad held a Financial Earnings conference call for investors. Myriad's executives represented that "Myriad once again delivered double-digit top and bottom line growth," including year-over-year increases of 17% in revenues and 31% in adjusted earnings per share. *Q3 2014 Myriad Genetics Earnings Conference Call—Final*, Tr. No. 050614a5353732.732 (May 6, 2014) (LEXIS, FD (Fair Disclosure) Wire) (hereinafter "3Q14 Conference Call"). Myriad experienced similarly rosy financial results in the preceding quarter, covering October through December 2013. *See Q2 2014 Myriad Genetics Earnings Conference Call – Final*, Tr. No. 020414a5278975.775 (Feb. 4, 2014) (LEXIS, FD (Fair Disclosure) Wire) (hereinafter "2Q14 Conference Call") (stating that Myriad "developed another exceptional quarter" and experienced "record revenues," and that all of Myriad's product groups—including the *BRCA* tests at issue here—"experience[d] solid growth rates this quarter, reflecting continued strong demand").

As to loss of market share due to the competition, its executives admitted that in the second quarter, Myriad experienced only "modest, incremental [market] share loss" in the genetics portion of Myriad's oncology business (*i.e.*, the portion that includes *BRCA* testing), which Myriad did not consider "*significant*" in view

of Myriad's second-quarter revenue growth. 2Q14 Conference Call, *supra* (emphasis added). Myriad continued this message in the third quarter, which "saw only a small additional decrease in market share in the genetic segment [of oncology] that represents 15% of our business," and emphasized that "[w]e believe our increased selling efforts into this channel, as well as the introduction of myRisk, will stabilize our future market share." 3Q14 Conference Call, *supra*.

Myriad's predictions of significant price erosion attributable to private third-party payors and CMS similarly failed to materialize. Private payors represent about 75% of Myriad's revenues, and Myriad reported to investors there have been "*no material changes* in selling price in the private pay segment," 2Q14 Conference Call, *supra*, and revised its 2014 revenue guidance upward on the express "assum[ption]" that there will be "*no material declines* in private pay pricing," 3Q14 Conference Call, *supra* (emphasis added).

On CMS price erosion, CMS initially reduced reimbursement amounts for *BRCA* testing from $2,700 to $1,438.14 effective January 1, 2014. (A60.) CMS subsequently increased that reimbursement amount to $2,200 effective April 1, 2014, *see CMS Gapfill Pricing Inquiries*, http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Gapfill-Pricing-Inquiries.html ("[W]e are revising the median price for CPT code 81211 to $2,200.00…") (last visited May 30, 2014); *see also* 3Q14 Conference Call, *supra* ("As you are aware,

Medicare recently increased its calendar year 2014 price for BRACAnalysis by 37%. Consequently, going forward, this impact will be less significant.").

The harm is far from *irreparable* even if the minimal price erosion is proven to be caused by competitors such as Ambry because it can be fully compensated by money damages. Myriad has already estimated for investors that the Medicare price reduction resulted in a year-over-year reduction of 6% in its third-quarter Oncology segment revenue, a figure easily calculable. *Id.*

This Court can and should take judicial notice of these recent admissions and developments. *See Brodsky v. Yahoo! Inc.*, 630 F. Supp. 2d. 1104, 1111 (N.D. Cal. 2009) (taking judicial notice of earnings call transcripts). The foregoing developments and admissions by Myriad in the seven months since the district court received evidence confirm that Myriad has not experienced the "substantial and immediate irreparable injury" required for preliminary injunctive relief. *Apple Inc. v. Samsung Elecs. Co.*, 695 F.3d 1370, 1374 (Fed. Cir. 2012).

II. THE DISTRICT COURT CORRECTLY FOUND THAT THERE ARE SUBSTANTIAL QUESTIONS REGARDING THE PATENT ELIGIBILITY OF MYRIAD'S COMPOSITION PRIMER CLAIMS

In adjudicating the patent eligibility of Myriad's '282 and '492 patents primer DNA sequence claims, the district court made detailed findings of fact to which it applied two lines of reasoning: *AMP III* by itself (A76-82) and the court's "independent reading of *AMP [III]*, *Funk Bros.*, and *Chakrabarty*." (*Id.* at 82-88.)

Under both lines of reasoning, the court concluded that a substantial question exists whether the primer claims are patent eligible.

Myriad neither directly challenges the district court's reasoning nor provides any reasons why the district court's findings of fact are clearly erroneous, and instead resorts to a test for patent-eligibility that improperly rests on a utility component. A correct reading of the controlling case law in view of the district court's findings of fact reveals the errors in Myriad's arguments. In any event, Myriad's primer claims are not patent eligible even under the incorrect standard Myriad urges this Court to adopt.

A. The District Court's Unchallenged Findings of Fact Conclusively Demonstrate that the Claimed Primers Are Indistinguishable from Natural DNA in Form, Information Content, and Function

The district court found that the composition claims directed to the sequence structures of a pair of DNA primers "derived from" or "isolated from" the *BRCA1/2* genes sequences are indistinguishable from the natural *BRCA* DNA in form, informational content, and function. Those factual findings include:

- "[T]he claimed primers [] have the same sequences as naturally occurring *BRCA* DNA," and "[t]his is true whether the nucleotide sequence is found in genomic DNA, or used in a primer or probe." (A84; *see also* A9528-29, A9531, A9565-71.)
- "[T]he claimed primers must share a structural similarity with the naturally occurring DNA sequence if the primers are to serve the purpose claimed in Plaintiffs' patents." (A83; *see also* A9528-29, A9531, A9565-71.)

- "[The claimed primers] function like natural DNA during replication, pairing predictably according to Watson-Crick principles. *See* Pribnow 2nd Decl. at ¶ 11 (primers' 'utility depends on the fact that a DNA segment used as a primer is structurally and functionally the same as a 'native' genomic DNA segment of the same sequence and length.')." (A87; *see also* A9527-29.)

- "The sequence of the primer is necessarily complementary to the target sequence, so that the bases of the primer and the bases of the target sequence bind to each other. [Kay Decl. ¶ 29]." (A13; *see also* A9527-29.)

- "The court agrees with the observation of [Ambry's] expert Dr. David Pribnow that 'the way [Myriad] uses 'design' implies that a scientist creates a *BRCA* primer sequence in a vacuum (or 'from scratch'). This is not accurate, scientifically. Primers are designed in reference to the natural[ly]-occurring sequence that is desired to be replicated following Watson-Crick base pairing.' Pribnow 2nd Decl. at ¶ 6." (A82 n.37.)

- "Because the primers in a pair are designed to 'hybridize' to their *BRCA* primer binding sites per Watson-Crick base pairing rules, the *BRCA* primers must contain sequences identical to the *BRCA* sequence directly opposite its binding sites. *Id*." (A14; *see also* A9527-29.)

Myriad does not contend these findings are clearly erroneous.

B. The District Court's *AMP III* Analysis Is Correct

In *AMP III*, a unanimous Supreme Court broadly held that "genes and the information they encode are not patent eligible under § 101 simply because they have been isolated from the surrounding genetic material" and that DNA, whether physically excised from natural DNA or chemically synthesized in a lab, is patent ineligible if "indistinguishable from natural DNA." 133 S. Ct. at 2119-20.

The district court's unchallenged findings of fact confirm that the claimed pairs of DNA primers "isolated" or "derived" from the *BRCA1/2* genes are plainly

"indistinguishable from natural DNA." *See id*. The plain language of the asserted primer claims requires that the DNA primer's sequence be "isolated from" or "derived from" human chromosomes, *i.e*., be identical to a portion of the *BRCA* DNA sequence from the human chromosome, expressly invoking the Supreme Court's *AMP III* decision on "isolated DNA."[6] The district court's unchallenged finding is that "the claimed primers [] have the same sequences as naturally occurring *BRCA* DNA." (A84.)

Myriad provides two main arguments for why *AMP III* does not render its primer claims patent ineligible, neither of which withstands scrutiny. *First*, Myriad argues that the claimed primers are patent eligible merely because scientists select the portion of the natural DNA to chemically synthesize in the laboratory. (Myriad Br. at 48-50.) But how the claimed primers are made is irrelevant; rather, the question under *AMP III* is whether the primer compositions themselves contain the same sequence as "derived" from or "isolated" from natural DNA. As the district court noted, "[a]t every step, the *AMP* courts understood that the isolated DNA at issue included both extracted genomic DNA *as well as*

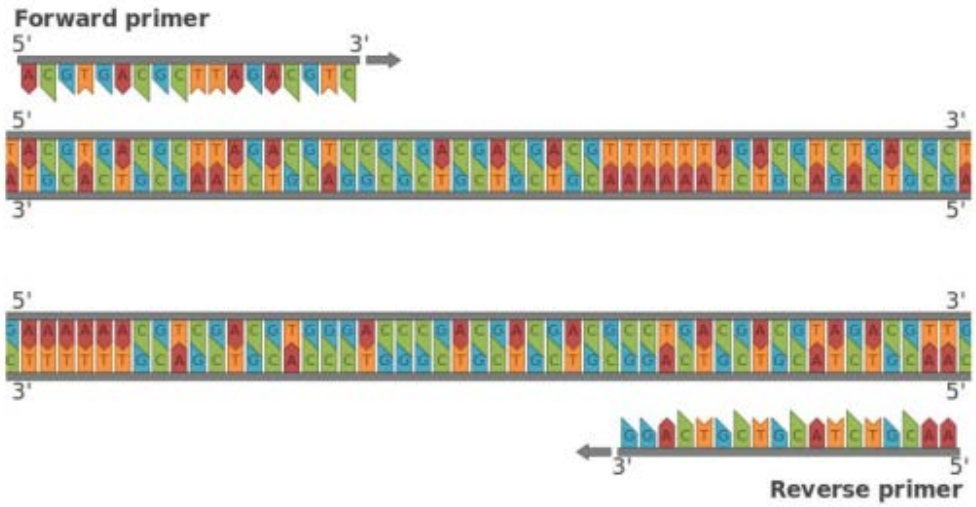
[6] Claims 16 and 17 require that the DNA primer sequences be "derived from" the human chromosome, which encompasses sequences "isolated" from the chromosome, as the district court found (the '492 patent recites the sequences are "isolated from" the human chromosome). (A84.) As such, the claim is invalid for containing patent-ineligible subject matter. *AMP I*, 702 F. Supp. 2d at 230, n.52 ("To the extent a claim reads on unpatentable subject matter, the entire claim must be deemed invalid.") (*citing Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985).

synthetic DNA." (A76 (emphasis added); *see also* A82; *AMP I*, 702 F. Supp. 2d at 217; *AMP III*, 133 S. Ct. at 2114-15.)

Each *AMP* court understood that chemically synthesized DNA could constitute "isolated DNA" because Myriad consistently took that position. Myriad argued to the Supreme Court that a primer is a single-stranded segment of *isolated DNA* that can "prime" a DNA reaction, *e.g.*, in amplification or sequencing, and that this new utility rendered its isolated DNA claims patent eligible. (*E.g.*, A6223 ("*As a 'primer,' the isolated DNA molecule* is used in a reiterative process called a polymerase chain reaction ('PCR')."") (emphasis added); A9572-74.) Myriad also presented expert testimony in *AMP I* that short, chemically synthesized primers (and probes) comprised "isolated DNA" within the meaning of its patents. (A6021-23 ¶¶ 134-38; *see also* A9568-70.)

The *AMP III* Court's recognition that chemically synthesized DNA is not always patent eligible is apparent from its holding specific to cDNA. The Court recognized cDNA is made by a "lab technician" and that cDNA "is patent eligible under § 101, *except insofar as very short series of DNA may have no intervening introns to remove when creating cDNA. In that situation, a short strand of cDNA may be indistinguishable from natural DNA*." *AMP III*, 133 S. Ct. at 2119 (emphasis added). Put differently by the district court, "[i]f cDNA—which is clearly synthetic—is sometimes patent ineligible, then implicit in the Supreme

Court's decision is the conclusion that not all synthetic DNA is patent eligible." (A80.) The DNA primer claims here recite a composition of matter whose structure is defined by reference to the natural gene sequence. How the composition is made is irrelevant unless it reflects a structural difference from the natural sequences. The factual findings that Myriad does not dispute confirm such structural difference is lacking. Indeed, Myriad represented that the primer sequences were the same as a portion of the natural sequence in the following diagram from its preliminary injunction moving papers:



(A1904.)

Second, Myriad argues that the claimed DNA primers are neither genes nor encode information and thus avoid the *AMP III* holding that "genes and the information they encode are not patent eligible under § 101 simply because they have been isolated from the surrounding genetic material." (Myriad Br. at 58

(quoting 133 S. Ct. at 2120).) Myriad's contention fails because the Supreme Court understood that at issue there were DNA molecules that do not encompass an entire gene, such as the probes and primers to which Myriad repeatedly referred throughout that litigation. Among the claims found patent ineligible in *AMP III* are those covering DNA segments as short as 15 nucleotides, which is even shorter than many probes or primers:

> 1. An isolated DNA coding for a *BRCA1* polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.
>
> 5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.

(A241.) The Court also recognized that scientists could isolate only parts of genes. *AMP III*, 133 S. Ct. at 2112 ("Scientists can, however, extract DNA from cells using well known laboratory methods. These methods allow scientists to isolate specific segments of DNA—for instance, a particular gene *or part of a gene*.") (emphasis added). As for Myriad's contention here that its primers do not encode information, the district court's unchallenged findings demonstrate that a sequence of DNA of any length contains information. (*See* II.A., *supra*; *see also* A8887 at 105:1-17.)

The district court recognized that the claimed primers are "isolated" or "derived" from the identical natural DNA sequences and therefore are governed by *AMP III*. (A76-82.) The district court considered and correctly rejected Myriad's

argument that its primers are patent eligible because they are chemically synthesized. The district court's holding based on *AMP III* should not be disturbed.

C. The District Court's Conclusion Under *Chakrabarty* and *Funk Brothers* that the Claimed Primers Are Patent-Ineligible Products of Nature Is Correct and Should Not Be Disturbed

Chakrabarty and *Funk Brothers* also compel finding the primer claims to be patent ineligible. *Chakrabarty* addressed the patent eligibility of a genetically engineered bacterium not found in nature that could break down crude oil. 447 U.S. at 305-10. *Funk Brothers* addressed the patent eligibility of a mixture of several strains of naturally occurring bacteria, where the patentee had altered no strain of bacteria and the patentee merely discovered that he could combine the naturally occurring strains into a new and useful mixture. 333 U.S. at 128-29. The Court found Chakrabarty's non-natural bacterium patent eligible but reached the opposite result regarding the mixture of natural bacteria in *Funk Brothers*. *Compare Chakrabarty*, 447 U.S. at 310 *with Funk Bros.*, 333 U.S. at 131-32.

The *AMP III* Court applied these cases to find contested Myriad DNA composition claims patent-ineligible. Myriad and the Supreme Court there both recognized *Chakrabarty* as "central" to the analysis, *e.g.*, that to be patent eligible the claimed isolated DNA of as few as 15 nucleotides must have "markedly different characteristics from any found in nature." *AMP III*, 133 S. Ct. at 2117.

In finding Myriad's claims patent ineligible, the Court reasoned that unlike Chakrabarty, "Myriad did not create anything" and merely discovered the *BRCA* gene sequences and portions thereof. *Id.* The fact that Myriad merely discovered the gene sequences rather than create new gene sequences also compelled the Court to find Myriad's claims patent ineligible under *Funk Brothers*. *Id.*

Chakrabarty and *Funk Brothers* compel the same conclusion here, whether focusing on structure or function to assess whether the claimed DNA primer composition sequences have "markedly different characteristics from any found in nature." *Chakrabarty*, 447 U.S. at 310. The district court's findings of fact make clear that the claimed primers are structurally similar to what is found in nature. (*See* II.A., *supra*.) As one example, the district court found—and Myriad does not dispute—that the claimed primers have the "same sequence as naturally occurring *BRCA* DNA"; otherwise, the primers could not serve the purpose of Myriad's claims. (A83-84.) Likewise, the district court's unchallenged findings of fact confirm that the claimed primers have similar utility as what is found in nature. (*See* II.A., *supra*.) The district court found that "during PCR, the primers function similarly to genomic DNA undergoing replication in the human body." (A85.)

Myriad's argument for why the non-natural bacterium in *Chakrabarty* is similar to its DNA primer sequences obtained from the natural sequence does not withstand scrutiny. Myriad contends that "the claimed primer pairs are designed

and made by scientists in the laboratory" which Myriad believes likens them to the bacterium Chakrabarty created in his laboratory. (Myriad Br. at 48.) The district court's unchallenged findings of fact undercut this argument, because they show that the scientist does not actually "design" a new primer sequence. (*E.g.*, A82 n.37; A9528.) Rather, the scientist "creates" a *BRCA* primer by deciding which natural *BRCA* nucleotide sequence to include in the primer:

> Scientists *create* primers. In so doing, they consider primer size and other aspects, such as the exact portion of the DNA segment targeted. (Pribnow 2nd Decl. at ¶ 8.) *These considerations are dictated by the nucleotide sequence of the DNA segment to which the primer is intended to bind. Id.*

(A14.) (emphasis added). *See also* A82 n.37 (rejecting as matter of fact Myriad's "design" contention). (A7613-14 ¶¶ 5-7.) *Chakrabarty* does not save Myriad's claims because there, unlike what Myriad claims here, Chakrabarty's "discovery [was] not nature's handiwork, but his own…." *See* 447 U.S. at 303.

Myriad also contends that "[t]he fact that the claims are directed to primer *pairs* moves them even further from the realm of products of nature." (Myriad Br. at 49.) According to Myriad, because the primers are "designed" as a pair renders them patent eligible, even though the district court found that each primer is identical to the natural DNA sequence from which it was isolated or derived. *Funk Brothers* illustrates why this argument fails, for there the Supreme Court found

patent ineligible a mixture of different strains of bacteria where the patentee altered none of the strains (*i.e.*, he just mixed several naturally occurring strains):

> Each of the species of root-nodule bacteria [in the combination] . . . infects the same group of leguminous plants which it always infected. No species acquires a different use. The combination of species produces no new bacteria, no change in the six species of bacteria, and no enlargement of the range of their utility. Each species has the same effect it always had. The bacteria *perform in their natural way*. Their use in combination does not improve in any way their natural functioning. *They serve the ends nature originally provided* and act quite independently of any effort of the patentee.

333 U.S. at 131 (emphasis added). Likewise, combining one patent-ineligible primer with a second patent-ineligible primer does not make patent-eligible the combination of a pair of DNA primer sequences "isolated" or "derived" from the natural DNA sequence.

D. The Primer Claims Are Invalid Even Under Myriad's Incorrect Test for Patent Eligibility

Myriad urges the Court to find a composition is patent ineligible if "both its structure *and utility* are as in nature, unaltered by man." (Myriad Br. at 45.) In other words, if a product of nature has a structure or utility altered from that which is observed in nature, then it is patent eligible.

None of the cases relied on by Myriad imposes this requirement in this way. The Supreme Court in *Funk Brothers* found that the claimed invention had altered

utility even though it was a patent-ineligible product of nature.[7] *See* 333 U.S. at 131 ("There is, of course, an advantage in the combination. … But a product must be more than new and useful to be patented; it must also satisfy the requirements of invention or discovery.") (cited in Myriad Br. at 45.) In *Chakrabarty*, there was utility in a genetically engineered organism that can break down crude oil, but that utility did not confer patent-eligibility alone. 447 U.S. at 310 (discussing utility but finding patent-eligibility because claimed bacterium was patentee's rather than nature's handiwork) (cited in Myriad Br. at 45-46.) *AMP III* mentions "utility" only once, and only because "new plant breeds were eligible for utility patents under § 101" in rejecting Myriad's argument that "the PTO's past practice of awarding gene patents is entitled to deference…" 133 S. Ct. at 2118 (cited in Myriad Br. at 46-47.)

Though contrary to *Chakrabarty* and *AMP III*'s "markedly changed characteristics" test, Myriad's primer claims fail to satisfy even Myriad's improper framework of an "unaltered" structure and utility. The claimed primers are structurally similar to natural DNA. (*See* II.A., *supra*.) The utility of the claimed primers is also observed in nature, as demonstrated by other undisputed findings of

[7] In *Mayo*, the Court also noted that the machine-or-transformation test cannot "[t]rump 'the law of nature' exclusion." 132 S. Ct. at 1302-03 (citing *Bilski v. Kappos*, 130 S. Ct. 3218, 3225-27 (2010)). Thus, even though a useful transformation may occur, it does not end the inquiry of patent-eligibility.

fact reproduced above describing that the claimed primers function like natural DNA and owe their utility to Watson-Crick base pairing. (*Id*.)

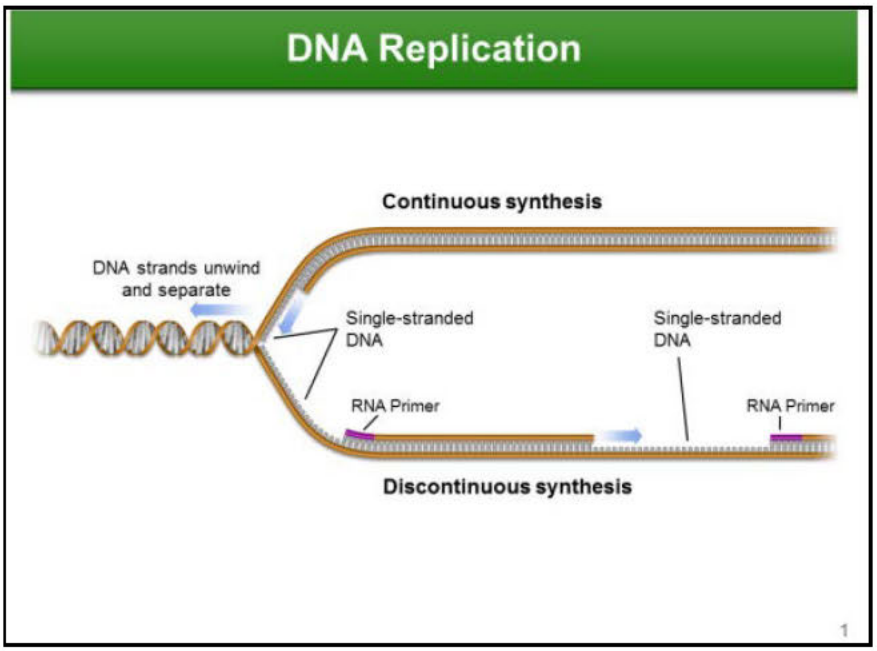
Myriad contends its primers have a utility distinct from natural DNA or its fragments, namely, "priming," or "serving as a starting material for a DNA polymerization process." (Myriad Br. at 50-54.) The district court's undisputed findings of fact are to the contrary. The district court found:

> "[The claimed primers] function like natural DNA during replication, pairing predictably according to Watson-Crick principles. *See* Pribnow 2nd Decl. at ¶ 11 (primers' ***"****utility depends on the fact that a DNA segment used as a primer is structurally and functionally the same as a 'native' genomic DNA segment of the same sequence and length.*").

(A87.) (emphasis added.)

The fact that during DNA replication cells use RNA primers to initiate replication (as Myriad concedes, *see* Myriad Br. at 51) further confirms that the actual utility of the claimed primers is the ability to Watson-Crick base pair rather than the fact that they are short segments of chemically synthesized DNA. (A9527-28.) PCR (which uses DNA primers) mimics *in vivo* DNA replication in which RNA primers are assembled on the DNA strand being replicated through Watson-Crick base pairing. (*See* A7616-18 ¶¶ 14, 15, 17.) "Priming" merely requires that a nucleic acid—either DNA or RNA—be complementary to the target sequence such that the replication or amplification machinery can initiate those processes. If there is no Watson-Crick base pairing according to the laws of

nature, then the claimed primers will not work.[8] Both the structure and the "utility" of Myriad's claimed primer sequences mirror nature. RNA primers are depicted below in this figure from Dr. Pribnow's second declaration:



(A7617 ¶ 16.)

None of Myriad's arguments compel disturbing the district court's holding that Ambry had raised a "substantial question" of patent-eligibility.

[8] The USPTO's guidance is in accord. *See* U.S. Patent & Trademark Office, *Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena & Natural Phenomena & Natural Products* 11 *("Guidance")*, *available at* www.uspto.gov/patents/law/exam/myriad-mayo_guidance.pdf (a "pair of primers" is not patent eligible because the primers are not "markedly different from what exists in nature" because the structure and sequence "has not been altered" and the two primers have the same function "as their natural counterpart DNA, *i.e.*, to hybridize to their complementary nucleotide sequences").

III. MYRIAD'S '441 PATENT CLAIMS BECOME MOOT ON AUGUST 12, 2014, DUE TO JUDICIAL ESTOPPEL, AND IN ANY EVENT NOT LATER THAN JANUARY 20, 2015, WHEN THE '441 PATENT ACTUALLY EXPIRES

The expiration of a patent moots any pending appeal from the denial of an injunction against infringement. *See, e.g.*, *Metaullics Sys. Co. v. Cooper*, 100 F.3d 938, 939 (Fed. Cir. 1996), *abrogated on other grounds*, *Cyber Corp. v. FAS Technologies, Inc.*, 138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc). Myriad has argued repeatedly that the patents invoked in its preliminary injunction motion "begin to expire" in August 2014, and has tacitly acknowledged that (as logic would dictate) this referred to the earliest-expiring patent(s), in this case, the '441 patent. Moreover, Myriad's representation contributed to the finding of irreparable harm.

The '441 patent should be deemed to expire on August 12, 2014, by operation of judicial estoppel, even if Myriad now agrees with Ambry's recent conclusion that the '441 patent expires on January 20, 2015. *See Eastman v. Union Pac. R.R.*, 493 F.3d 1151, 1156 (10th Cir. 2007) (judicial estoppel applies where a party (a) takes a "subsequent position [that is] 'clearly inconsistent' with its former position"; (b) "succeeded in persuading a court to accept that party's former position, 'so that judicial acceptance of an inconsistent position in a later proceeding would create the *perception* that either the first or the second court was misled'"; and (c) "would gain an unfair advantage in the litigation if not

estopped"); *see also Wang Labs., Inc. v. Applied Computer Scis., Inc.*, 958 F.2d 355, 358 (Fed. Cir. 1992) (regional circuit law controls application of judicial estoppel in patent disputes).

Myriad (i) repeatedly represented to the district court and this Court that its patents "begin to expire" in August 2014, (ii) did not correct the district court's determination, for Myriad's claim of irreparable harm, that this comprised the '441 patent, and (iii) would now gain unfair advantage if it may deny mootness by taking advantage of Ambry's recent discovery of the actual January 20, 2015 expiration date. The requirements for judicial estoppel are satisfied here.

It is virtually certain that this Court will not issue its decision by August 12, 2014, in which case Myriad's appeal as to the '441 patent will be moot under judicial estoppel. Even if Myriad is not judicially estopped from denying mootness, this appeal and the preliminary injunction proceeding as to the '441 patent will indisputably become moot on January 20, 2015.

IV. THE DISTRICT COURT PROPERLY FOUND THAT A SUBSTANTIAL QUESTION OF PATENT INELIGIBILITY EXISTS AS TO THE ASSERTED '441 PATENT METHOD CLAIMS

The district court found a substantial question of patent eligibility as to dependent method claims 7 and 8 of the '441 patent for two primary reasons after analyzing the applicable law. (A88-93.) *First*, the district court concluded that besides the newly discovered but patent-ineligible subject matter (the *BRCA1* and

BRCA2 sequences and patent-ineligible abstract mental comparison), the claims include only "well-understood, routine, conventional activity previously engaged in by scientists at the time of Myriad's Patent Applications." (A93-95.) These routine concepts are amplification, sequencing and hybridization. *Second*, based on the facts before it, the court held that allowing Myriad's method claims would preempt all practical uses of the patent-ineligible subject matter in the claims, namely the ability to compare *BRCA* sequences. (A95-100.) These conclusions rest on factual findings that (i) the method claims lack any inventive concept and recite routine and well-known steps, and (ii) the method claims effectively preempt the practical application of the patent-ineligible subject matter of comparing two *BRCA1* DNA sequences.

A. The District Court's Analysis Regarding Lack of an Inventive Concept is Correct

1. The Court's Factual Findings that the Asserted Inventive Concepts in the Method Claims Are the *BRCA1* and *BRCA2* Sequences and Their Comparison, and that the Method Claims Otherwise Set Forth Well-Understood, Routine and Conventional Activity Are Not Clearly Erroneous

The district court made factual findings that confirm that the method claims contain no inventive concept apart from the discovery of the *BRCA* gene sequence and their comparison. Those factual findings include:

- "The claims contain no otherwise new process for designing or using probes, primers, or arrays beyond the use of *BRCA1* or *BRCA2* sequences

in those processes." (A93; *see also* A9595-96.)

- "'Aside from the patent ineligible, naturally occurring nucleotide sequence of the *BRCA1* and *BRCA2* genes, the other steps set forth in the Method Claims are conventional activities that were well-understood and uniformly employed by those working with DNA at the time Myriad applied for its patents: DNA amplification, sequencing, comparisons, detecting alterations in sequences, and hybridizing probes to alleles.' Tait Decl. at ¶ 37." (A94; s*ee also* A9595-96.)

- "The laboratory materials, reagents, and protocols to accomplish these activities were well known and widely available in the art by the time the first August 1994 patent application corresponding to the asserted patents had been filed. *Id*. at ¶ 31." (A94-95; *see also* A9567-68, A9595-96.)

- "Any scientist engaged in obtaining the sequence of a gene in a patient sample would rely on these techniques." (A95; *see also* A9595-96.)

- "[T]he '282 Patent provides that 'the practice of the present invention employs, unless otherwise indicated, conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA, genetics, and immunology.' '282 Patent col.25 ll.50-55; Tait 2nd Decl. at ¶ 9; see also '441 Patent col.17 ll.20-27 ('These methods are well known and widely practiced in the art.')." (A95; *see also* A9595-96.)

These well-known and routine concepts are generically captured in the words of claims 7 and 8, which depend from claim 1 that was adjudicated as a patent-ineligible "mental process of comparing two [*BRCA*] nucleotide sequences." *AMP II*, 689 F.3d at 1334-35. Claims 7 and 8 recite:

> 7. The method of claim 1 wherein a germline nucleic acid sequence is compared by hybridizing a *BRCA1* gene probe which specifically hybridizes to a *BRCA1* allele to genomic DNA isolated from said sample and detecting the presence of a hybridization product wherein a presence of said product indicates the presence of said allele in the subject.

> 8. The method of claim 1 wherein a germline nucleic acid sequence is compared by amplifying all or part of a *BRCA1* gene from said sample using a set of primers to produce amplified nucleic acids and sequencing the amplified nucleic acids.

(A348.) Claims 7 and 8 add to invalid claim 1 only the uses of probes and primers that embody the patent-ineligible *BRCA1* DNA sequence in methods that the district court determined were well known and widely practiced in the art. The '441 patent specification confirms as well that "[t]hese methods are well known and widely practiced in the art." (A95 (quoting A279 at 17:20-27).) So, too, do undisputed factual findings. (A93-95.)

The Supreme Court in *AMP III* found that Myriad's "principal contribution was uncovering the precise location and genetic sequence" of the *BRCA* genes and noted, "the location and order of the nucleotides [of *BRCA1* and *BRCA2*] existed in nature before Myriad found them." 133 S. Ct. at 2116. The Court recognized that Myriad created no "innovative method[s]" while searching for *BRCA* gene sequences:

> Had Myriad created an *innovative* method of *manipulating genes* while searching for the *BRCA1* and *BRCA2* genes, it could possibly have sought a method patent. But the processes used by Myriad to isolate DNA . . . at the time of Myriad's patents "were well understood, widely used, and fairly uniform insofar as any scientist engaged in the search for a gene would likely have utilized a similar approach."

Id. at 2119-20 (quoting *AMP I*, 732 F. Supp. 2d at 202-03). The claim language, the specification, the *AMP II* and *AMP III* decisions, and the findings of fact

grounded in expert testimony all confirm the lack of any innovative concept in the two method claims that Myriad's unsupported arguments cannot conceal.

2. Myriad's '441 Patent Claims 7 and 8 Are Patent-Ineligible Because They Violate the Rule that Claims Incorporating Natural Laws Must Recite Inventive Concepts

Myriad does not dispute its method claims contain ineligible subject matter; nor does Myriad provide any reason to disturb the factual findings showing the method claims contain no additional inventive concept. The question of patent eligibility of the two '441 patent method claims is answered by a straightforward application of *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012).

Mayo reiterates the requirement for an "inventive concept" that is "significantly more" than claimed patent-ineligible subject matter. The claim at issue in *Mayo* recited a method for optimizing using a thiopurine drug to treat autoimmune diseases that included the steps of "administering" the drug and "determining" the level of a drug metabolite in the body and adjusting the dosage accordingly. *Id*. at 1295. The law of nature being "applied" was that certain concentrations of the metabolites in the blood likely meant that the dosage of the drug was either ineffective or harmful. *Id.* at 1296. The Court held that the steps purporting to apply the law of nature by "administering" and "determining" "involve[d] well-understood, routine, conventional activity previously engaged in

by researchers in the field." *Id.* at 1294. The Court articulated the rule that "a process that focuses on the use of a natural law [must] also contain other elements or a combination of elements, sometimes referred to as an '*inventive concept*,' sufficient to ensure that the patent in practice amounts to *significantly more* than a patent upon the natural law itself." *Id*. (emphasis added) (citing *Flook*, 437 U.S. at 590 and *Bilski*, 130 S. Ct. at 3230). Accordingly, the thiopurine claim at issue in *Mayo* was not patent eligible.

The requirement that claims incorporating a natural law must also recite an "inventive concept" existed long before *Mayo*, as illustrated by *Mayo's* discussion of *Diehr* and *Flook*. The Supreme Court relied on these two earlier cases to reinforce its conclusion of patent-ineligibility and also to highlight the type of subject matter that could satisfy the "inventive concept" requirement.

At issue in *Diehr* was the patent-eligibility of a new and novel process for molding uncured rubber into cured, molded products. The *Diehr* method utilized a mathematical equation—itself not patent eligible—but applied that equation in a *novel, unconventional way* that was patent eligible. 450 U.S. at 177-79. *Mayo* recognized that "[*Diehr*] nowhere suggested that all these steps, or at least the combination of those steps, were in context obvious, already in use, or purely conventional." 132 S. Ct. at 1299.

At the other end of the spectrum of the patent eligibility of claims incorporating natural laws is *Flook*. There the Court held as unpatentable subject matter a method claim for adjusting "alarm limits" in the catalytic conversion of hydrocarbons. The Court found that that alarm values that must be recalculated and recomputed and the use of computers for "automatic monitoring-alarming" were all "well known, to the point where, putting the formula to the side, there was no 'inventive concept' in the claimed application of the formula." *Id.* at 1299 (quoting *Flook*, 437 U.S. at 586). As *Mayo* observed, "'post-solution activity' that is purely 'conventional or obvious,' the [*Flook*] Court wrote, 'can[not] transform an unpatentable principle into a patentable process.'" *Id.* (quoting 437 U.S. at 589-90). The claim at issue in *Flook* was patent ineligible because it lacked any inventive concepts.

The district court concluded, because Myriad could not show otherwise, that claim 7 and 8 of the '441 patent contained no inventive concept other than the patent-ineligible *BRCA* DNA sequence and its mental comparison to another *BRCA* sequence. "At bottom, Plaintiffs ask the court to find that obtaining knowledge of the naturally occurring *BRCA1* and *BRCA2* sequences is somehow an inventive step sufficient to render the Method Claims patent eligible. This cannot be." (A95.)

3. None of Myriad's Arguments Compel Disturbing the District Court's Conclusions That a Substantial Question of Patent Eligibility Exists for Want of Inventive Concept

Myriad advances four main reasons the district court purportedly committed legal error by finding a lack of inventive concept, none of which withstands scrutiny.

First, Myriad contends that claims 7 and 8 of the '441 patent "[(i)] do not purport to claim ownership of the *BRCA1* gene sequence itself, [(ii)] nor do they repeat claim 1's error of reciting simply an abstract comparison." (Myriad Br. at 28.) These arguments fail. Myriad's contention of "no ownership" over the sequence itself is belied by the district court's findings that to access the gene, one must use probes or primer tools to obtain the sequence of the genetic material to perform the patent-ineligible *BRCA1* sequence comparison. *See* IV.B.1., *infra*.

Myriad's contention that claims 7 and 8 do not "repeat claim 1's error of reciting simply an abstract comparison" fails for similar reasons. As just noted, Myriad discovered the *BRCA* sequences as they existed in nature; Myriad neither created nor "manipulated" those sequences in a new way. *AMP III*, 133 S. Ct. at 2119-20. Myriad concedes it did not invent primers and probes. (Myriad Br. at 34.) A sequence comparison of patent-ineligible claim requires as predicates PCR and/or probe hybridization as recited in dependent claims 7 and/or 8. (A16-20.) Claims 7 and 8 claim the same abstract comparison recited in patent-ineligible

claim 1 because the data gathering steps of claims 7 and 8 must be performed to do so.

Second, Myriad contends that claims 7 and 8 of the ’441 patent are patent eligible because they are similar to claim 21 of the ’441 patent, which Judge Bryson posited in his concurring opinion in *AMP II* is patent eligible. (Myriad Br. at 16-17) (quoting *AMP II*, 689 F.3d at 1348) (Bryson, J., concurring in part and dissenting in part).

This argument fails for two reasons. Myriad contends that claims 7 and 8 of the ’441 patent are “remarkably similar to claim 21” based solely on attorney argument. (Myriad Br. at 17, 30.) Myriad accounts for none of the differences apparent on the faces of those claims, such as the fact that claim 21 requires a DNA probe to hybridize to isolated RNA whereas claim 7 (also a hybridization claim) requires a DNA probe to hybridize to isolated genomic DNA. (*Id*. at 17.)

Myriad overreaches by stretching Judge Bryson’s *dicta* in *AMP II* regarding claim 21 of the ’441 patent as patent eligible into a ruling of patent eligibility of claims 7 and 8. Claim 21 was not at issue during any stage of the *AMP* litigation or this litigation. No court has considered claim 21 in view of a proper record. The same holds true for the other claims Judge Bryson mentioned: claim 22 of the ’492 patent and claim 9 of the ’282 patent. Myriad’s attorney argument relying on Judge Bryson’s comment (and the Supreme Court’s *dicta* citation thereto) cannot

overturn the district court's conclusions grounded in undisputed factual findings. As the district court noted, Myriad overstates the significance of Judge Bryson's statement. (A88 n.38.)

Third, Myriad suggests this Court impliedly endorsed the eligibility of its asserted method claims because they recite "physical steps." (Myriad Br. at 31-32.) ("The method claims invalidated in *AMP [II]* were found patent ineligible because they covered only 'abstract mental process'—specifically, they recited abstract methods for comparing or analyzing gene sequences without any physical steps."). Physical steps are not enough by themselves to render eligible an otherwise ineligible abstract mental claim, as *Mayo* confirms by finding ineligible a method claim reciting physical steps of administering the drug and determining the resulting metabolite concentrations. 132 S. Ct. at 1295. What's more, *Mayo* further states that claims could be patent ineligible even if they met the machine-or-transformation test, the latter of which includes at least one physical step. *Id.* at 1302-03 (noting also that the "machine-or-transformation test" is an "'*important and useful clue*' to patentability" but does not "trump[] the 'law of nature' exclusion") (citing *Bilski*, 130 S. Ct. at 3225-27) (emphasis added in *Mayo*).

Fourth, Myriad argues that the district court erred in that it misapplied *Mayo* by not considering its method claims "as a whole." (Myriad Br. at 32-36.) The linchpin of this argument is that because the *BRCA* sequences were not known

until Myriad found them, claims reciting using probes and primers to amplify and detect those *BRCA* sequences could not have been known and therefore are patent eligible. (*Id.* at 34.) Myriad argues that the district court "carved" the claims into two pieces: the natural law and the remaining steps, and considered each in a vacuum. (*Id.* at 33.) According to *Myriad*, *Diehr* prohibits the district court's approach. (*Id.* at 33-34.)

There are two flaws with Myriad's argument. First, the district court understood it must consider the claims as a whole and did so, as noted earlier. (A92-95, 97-98.) Second, *Diehr* merely holds it "is inappropriate to dissect the claims into old and new elements and to then *ignore* the presence of the old elements in the analysis." 450 U.S. at 189 (emphasis added). Under this directive from *Diehr*, the district court did not "ignore" any elements as just discussed.

B. The District Court's Conclusion that the Method Claims Effectively Preempt Using the Patent-Ineligible Subject Matter Is Correct

The district court further concluded that Myriad's method claims are not patent eligible because they "essentially foreclose the most widely used means to study and test for *BRCA1* and *BRCA2* genes." (A95-99.) They would "risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries." 132 S. Ct. at 1294. The Court should not disturb this conclusion.

1. Myriad Has Not Challenged the District Court's Findings of Fact as to Preemption

The district court supported its conclusion by finding the following facts, none of which Myriad challenges[9] as clearly erroneous:

- "To study a gene, geneticists generally must amplify a given DNA sample. Kay Decl. at ¶ 31." (A96; *see also* A8998, A9567-68, A9570.)
- "The most widely used means to amplify DNA is through PCR, which requires primers. Kay Decl. at ¶ 32; Pribnow Decl. at ¶ 70." (A96; *see also* A9570.)
- "The PCR process was patented in 1987, and since that time it has been critically important to DNA testing. Pribnow Decl. at ¶ 74." (A96.)
- "Probes, like primers, are short segments of DNA capable of hybridizing to DNA segments according to Watson-Crick pairing. Pribnow Decl. at ¶ 85." (A96; *see also* A9593-94.)
- "PCR using primers and probe hybridization are the means needed to determine and compare *BRCA1* and *BRCA2* sequences, and to conduct *BRCA1* and *BRCA2* tests. Tait Decl. at ¶¶ 48-51." (A96; *see also* A9567-68, A9570.)

[9] Myriad states in its brief, "[t]he recited probe hybridizing and detection steps in claim 7, and primer amplification and sequencing steps in claim 8, are not inherent in any use of the *BRCA1* gene—they are not required to isolate the gene for study, they do not prohibit studying it in other ways." (Myriad Br. at 39.) Myriad does not dispute the district court's findings of fact, which, importantly, *rely on Myriad's own expert Dr. Kay***.** In fact, Dr. Kay confirmed during the preliminary injunction hearing that scientists need far more copies of the patients' *BRCA* genes for testing than the two copies that are present in each cell and that geneticists "need a method of amplifying DNA products," such as PCR. (A8998 at 216:5-15.) Instead, Myriad points the Court to two web pages in its brief at footnote 5 that purport to support its attorney argument that PCR and probe hybridization are not required to study the *BRCA* genes. This attempt to introduce some other means is insufficient to find the district court's holdings as clearly erroneous.

- "Aside from the patent ineligible, naturally occurring nucleotide sequence of the *BRCA1* and *BRCA2* genes, the other steps set forth in the Method Claims are conventional activities that were well-understood and uniformly employed by those working with DNA at the time Myriad applied for its patents. Tait Decl. at ¶ 37." (A94; *see also* A9593-96.)

- "The laboratory materials, reagents, and protocols to accomplish these activities were well known and widely available in the art by the time the first August 1994 patent application corresponding to the asserted patents had been filed. [Tait Decl. at ¶ 31]." (A94-95; *see also* A9593-96.)

Amplification and sequencing or detection of sequence by probes "are the means to determine and compare *BRCA1* and *BRCA2* sequences" (A96) and appending them to the patent-ineligible sequence comparison of claim 1 "risks disproportionately tying up the use of the underlying natural laws," *Mayo*, 132 S. Ct. at 1294, as the district court's factual findings confirm. Myriad has not shown these findings to be clearly erroneous.

2. The District Court Properly Applied the Law Prohibiting Preemption of a Natural Law or Abstract Ideas to These Unchallenged Findings of Fact

Claims incorporating natural laws or abstract ideas are not patent eligible unless they are "meaningfully restricted" to a particular technical application. *Ultramercial*, 722 F.3d at 1344 ("[T]he relevant inquiry is whether a claim, as a whole, includes *meaningful* limitations restricting it to an application, rather than merely an abstract idea.") (emphasis in original); *see also Mayo*, 132 S. Ct. at 1297 ("[Attempting] to limit the use . . . to a particular technological environment" cannot "circumvent[ ]" either "the prohibition against patenting abstract ideas" or

phenomena of nature.). *Mayo* also declared that "[i]f a law of nature is not patentable, then neither is a process reciting a law of nature, *unless that process* has additional features that provide practical assurance that the process *is more than a drafting effort designed to monopolize the law of nature itself*." 132 S. Ct. at 1297 (emphasis added). Thus, "[i]f, to implement the abstract concept, one *must* perform the additional step, *or the step is a routine and conventional aspect of the abstract idea*, then the step merely separately restates an element of the abstract idea, and thus does not further limit the abstract concept to a practical application." *Ultramercial*, 722 F.3d at 1348 (emphasis added).

The district court's findings of fact (i) identified the field (determination of patient *BRCA* gene sequences), and (ii) found that the claimed processes are widely used, and that Myriad's claims effectively appropriated the *BRCA* gene sequences. (A95-100.) The district court correctly found that Myriad's two method claims lack meaningful restrictions. Therefore, these claims are no more than a patent "drafting effort" to monopolize the law of nature or sufficiently restricted to a specific, innovative application as discussed in *Mayo*. *See* 132 S. Ct. at 1297.

Myriad's arguments to the contrary cannot disturb the district court's holding. Myriad first argues preemption is not a legitimate concern under Section 101. (Myriad Br. at 37.) The district court was right to address the issue as part of its overall Section 101 analysis. The *Mayo* Court warned that upholding the claims

at issue there "would risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries." 132 S. Ct. at 1294. So too here, the claims risk disproportionately tying up the ineligible subject matter of the *BRCA* DNA sequences and their comparison, as the district court found.

Myriad argues that the two claims "are not required to isolate the gene for study, and they do not prohibit studying it in other ways." (Myriad Br. at 39.) Notably, Myriad neither cites factual support for these broad generalizations, nor shows the district court's contrary factual findings to be clearly erroneous. Further, as stated in *Ultramercial*, "a claim is not meaningfully limited if its purported limitations provide no real direction, cover all possible ways to achieve the provided result [*i.e.*, the comparison], or are overly generalized." 722 F.3d at 1346. Claims 7 and 8, which incorporate claim 1, cover every practical application of the abstract idea of comparing gene sequences because they claim the means for detecting the gene sequence.[10]

[10] The USPTO's *Guidance* is consistent with the district court's conclusion. The USPTO found eligibility of a "method of amplifying" a target sequence where multiple narrowing and "meaningful" limitations are present, including temperature limitations, number of cycles and type of polymerase to be used. *Guidance* at 12-13. The '441 patent claims 7 and 8 contain no such meaningful restrictions on amplification, and the recited steps of amplification and sequencing are necessary in order to access the information for the patent-ineligible, abstract mental comparison of two *BRCA1* sequences.

Myriad further contends that claims 7 and 8 do not foreclose future sequence comparisons. (Myriad Br. at 39-40.) This is belied by Myriad's (i) failure to provide a complete evidentiary showing in the preliminary injunction process of how this is allegedly so, and (ii) by its assertion of infringement of claim 8 on technologies that use Next Generation Sequencing that did not exist at the time of Myriad's application was filed. (A2558 ¶ 2; A2563 ¶ 21.) Myriad's recitation to two web pages in footnote 5 of its Opening Brief fall far short of the showing necessary to disturb the district court's findings.

Myriad relies on *Morse* and *The Telephone Cases* to argue its claims are patent eligible. (Myriad Br. at 40-41.) Neither supports Myriad's position. As this Court noted in *Ultramercial* following its analyses of these same and other cases, "[i]f a claim covers all practical applications of an abstract idea, it is not meaningfully limited." 722 F.3d at 1345. The claims allowed in *Morse* and *The Telephone Cases* adhere to this principle because they were tied to specific applications of using electricity to communicate and did not foreclose all uses. *O'Reilly v. Morse*, 56 U.S. 62, 120 (1854); *Gottschalk v. Benson*, 409 U.S. 63, 69 (1972). Myriad's claims do not adhere to this principle because the method claims effectively appropriate the comparison of *BRCA* gene sequences through the general data gathering steps in claims 7 and 8.

Myriad faults the district court for finding that the appended steps of claims 7 and 8 are directed to "the most widely used means" to "study and test for *BRCA1* and *BRCA2* genes." (Myriad Br. at 43.) The court's finding of fact grounded in the record is not clearly erroneous because the two methods are a "routine and conventional aspect of the abstract idea" required to "implement the abstract concept" of comparing gene sequences. *See Ultramercial*, 722 F.3d at 1348. The limitations added to the patent-ineligible subject matter of claims 7 and 8 are merely "instructions [that] add nothing specific to the laws of nature other than what is well-understood, routine, conventional activity, previously engaged in by those in the field." *See Mayo*, 132 S. Ct. at 1299-1300.

Myriad also faults the district court for addressing the *Sequenom* district court opinion and attempts to distinguish it because the *Sequenom* DNA amplification and detection claims at issue involved a "known product of nature." (Myriad Br. at 43.) However, patent eligibility does not rest on whether the unpatentable subject matter is known or unknown, as *Mayo* confirms. There, the Court recognized the gatekeeper role of Section 101 "in evaluating the significance of additional steps" as compared to Section 102 and 103's anticipation or obviousness inquiries. *Id*. at 1304. This is because "one would suppose" that a limitation of a claim drawn to a law of nature would be patentable under Section 102 and 103 *where the law was unknown*, even if *the other steps were known*, since

a claim is not invalid unless all the elements of the claim are taught in the prior art. *Id.* The Section 101 inquiry under *Mayo* is not limited to obvious subject matter that effectively applied a *known* law of nature; rather, the inquiry extends to methods applying a previously unknown law of nature using "well-understood, routine, conventional activity already engaged in by the scientific community." *Id*. at 1298. There is no dispute in the record here that Myriad's claims do just that.[11]

The district court rightly found that claims 7 and 8 of the '441 patent are the "most widely used" means of obtaining the gene sequence information and that the claims unduly "construct a wall around the naturally occurring *BRCA1* and *BRCA2* genetic sequences, which … are naturally occurring, patent-ineligible subject matter." (A95, 98-99.) Allowing these claims to stand "would risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries." *See Mayo*, 132 S. Ct. at 1294. The claimed processes "too broadly preempt the use of a natural law," and the "steps in the claimed processes (apart from the natural laws themselves) involve well-understood, routine, conventional activity previously engaged in by researchers in the field." *See id.* The district court's finding of a "substantial question" should be affirmed.

[11] Myriad attacks the *Sequenom* decision now on appeal to this Court. Ambry requests that the Court review Arioso's May 5, 2014 Brief in *Ariosa Diagnostics, Inc., et al. v. Sequenom, Inc., et al.*, No. 14-1139 defending the *Sequenom* district court decision.

V. MYRIAD WAIVED ITS APPEAL AS TO THE '155 PATENT CLAIMS BY FAILING TO BRIEF THEM

Myriad waived its appeal by failing to offer *any* substantive argument to show that the district court abused its discretion in holding a substantial question exists whether claims 2 and 4 of the '155 patent are patent eligible. Myriad's discussion of that issue consists *in its entirety* of a single sentence in the middle of a footnote in the Statement of Facts: "Asserted method claims 2 and 4 of the '155 patent are similar to claims 7 and 8 of the '441 patent in that they employ primers to achieve their methods." (Myriad Br. at 20 n.3.)

Myriad's conclusory assertion of similarity—*in a single respect*—to claims of the '441 patent for which Myriad offered arguments fails entirely to "me[e]t its burden of showing a reasonable likelihood of success on the merits" as to the claims of the '155 patent. *See Chrysler Motors Corp. v. Auto Body Panels of Ohio, Inc.*, 908 F.2d 951, 954 (Fed. Cir. 1990). "In considering patent eligibility under § 101, *one must focus on the claims*. This is because a claim may 'preempt' only that which the claims encompass, not what is disclosed but left unclaimed." *Dealertrack, Inc. v. Huber*, 674 F.3d 1315, 1334 (Fed. Cir. 2012) (emphasis added).

Myriad performed no analysis to show these claims are the same subject matter. In fact, they are not as the '155 patent claims require as little as a single primer to use to compare the *BRCA* gene allegedly placed in the prior art by the

unrelated '441 patent inventors. A side-by-side comparison of the claim language itself confirms the differences and that Myriad has failed to carry its burden:

U.S. Pat. No. 5,753,441	U.S. Pat. No. 5,654,155
What is claimed is: 1. A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises comparing germline sequence of a BRCA1 gene or BRCA1 RNA from a tissue sample from said subject or a sequence of BRCA1 cDNA made from mRNA from said sample with germline sequences of wild-type BRCA1 gene, wild-type BRCA1 RNA or wild-type BRCA1 cDNA, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA of the subject from wild-type indicates an alteration in the BRCA1 gene in said subject.	
7. The method of claim 1 wherein a germline nucleic acid sequence is compared by hybridizing a BRCA1 gene probe which specifically hybridizes to a BRCA1 allele to genomic DNA isolated from said sample and detecting the presence of a hybridization product wherein a presence of said product indicates the presence of said allele in the subject.	2. A method of identifying individuals having a BRCA1 gene with a BRCA1 coding sequence not associated with breast or ovarian cancer comprising: a) amplifying a DNA fragment of an individual's BRCA1 coding sequence using an oligonucleotide primer which specifically hybridizes to sequences within the gene; b) sequencing said amplified fragment by dideoxy sequencing; c) repeating steps (a) and (b) until said individual's BRCA1 coding sequence is completely sequenced; d) comparing the sequence of said amplified DNA to the sequence of SEQ. ID. NO: 1; e) determining the presence or absence of each of the following polymorphic variations in said individual's BRCA1 coding sequence: AGC and ACT at position 2201, TTG and CTG at position 2430, CCG and CTG at position 2731, GAA and GGA at position 3232, AAA and AGA at position 3667, TCT and TCC at position 4427, and ACT and GGT at position 4956; f) determining any sequence differences between said individual's BRCA1 coding sequences and SEQ. ID. NO: 1 wherein the presence of any of the said polymorphic variations and the absence of a polymorphism outside of positions 2201, 2430, 2731, 3232, 3667, 4427, and 4956, is correlated with an absence of increased genetic susceptibility to breast or ovarian cancer resulting from a BRCA1 mutation in the BRCA1 coding sequence.

8. The method of claim **1** wherein a germline nucleic acid sequence is compared by amplifying all or part of a BRCA1 gene from said sample using a set of primers to produce amplified nucleic acids and sequencing the amplified nucleic acids.	**4.** A method of detecting an increased genetic susceptibility to breast and ovarian cancer in an individual resulting from the presence of a mutation in the BRCA1 coding sequence, comprising: a) amplifying a DNA fragment of an individual's BRCA1 coding sequence using an oligonucleotide primer which specifically hybridizes to sequences within the gene; b) sequencing said amplified fragment by dideoxy sequencing; c) repeating steps (a) and (b) until said individual's BRCA1 coding sequence is completely sequenced; d) comparing the sequence of said amplified DNA to the sequence of SEQ. ID. NO: 1; e) determining any sequence differences between said individual's BRCA1 coding sequences and SEQ. ID. NO: 1 to determine the presence or absence of polymorphisms in said individual's BRCA coding sequences wherein a polymorphism which is not any of the following: AGC or AGT at position 2201, TTG or CTG at position 2430, CCG or CTG at position 2731, GAA or GGA at position 3232, AAA or AGA at position 3667, TCT or TCC at position 4427, and AGT or GGT at position 4956; is correlated with the potential of increased genetic susceptibility to breast or ovarian cancer resulting from a BRCA1 mutation in the BRCA1 coding sequence.

VI. THE DISTRICT COURT DID NOT ABUSE ITS DISCRETION IN FINDING THAT THE BALANCE OF THE HARMS FAVORS AMBRY

The district court concluded that the balance of the harms requirement "tips slightly" in Ambry's favor (A103) because Ambry's "potential hardship in losing its entire business outweighs the hardship Myriad may suffer in terms of price erosion, market share, and the loss of the remainder of its patents' exclusive terms, which begin to expire in the coming months." (A102.) Myriad incorrectly asserts this finding rests entirely on the district court's antecedent determination that

Ambry had raised a substantial question concerning subject matter eligibility. (Myriad Br. at 60.)

The district court's determination that the balance of the hardships tipped slight in Ambry's favor was also based on the finding—that Myriad does not challenge—that Ambry "waited to launch *BRCA* testing until the years-long *AMP* litigation had concluded and had at least cast considerable doubt on the subject-matter eligibility of Myriad's patent claims. . . ." (A102.) The district court's determination is further bolstered by Myriad's misrepresentation of its patent term expiration that it weighed against Ambry's potential hardship. Absent that misrepresentation that infects its finding of irreparable harm, the district court might have determined that the balance of the hardships tipped more sharply in favor of Ambry.

VII. THE DISTRICT COURT DID NOT ABUSE ITS DISCRETION IN FINDING THE PUBLIC INTEREST IN EQUIPOISE

Myriad challenges the district court's determination that it failed to show that preliminary injunctive relief is in the public interest, arguing that protecting the right to exclude serves the public interest in personal medicine by encouraging risky investments in technological innovation. (Myriad Br. at 60.) But Myriad does not dispute two key findings by the district court—that Myriad's tests are more expensive and somewhat less available to the public than Ambry's comparable tests. (A104-05.) Myriad further does not dispute the finding that

since 2005, Myriad "has declined to publicly share critical information regarding its classifications of variants, including with its own patients." In so doing, "Myriad . . . turns much of our patent system on its head." (A106.) These unchallenged district court findings confirm the determination of public interest at equipoise was not an abuse of discretion.

CONCLUSION

For the foregoing reasons, Ambry respectfully requests that this Court affirm the district court's denial of a preliminary injunction.

June 2, 2014

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CERTIFICATE OF SERVICE

I hereby certify that I electronically filed Defendant-Appellee's Corrected Brief with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit by using the appellate CM/ECF system on June 9, 2014.

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UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Nos. 14-1361, -1366

UNIVERSITY OF UTAH, et al. v. AMBRY GENETICS

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